Modeling Cortical Spreading Depression

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Cortical spreading depression is a wave of electrical silence and biochemical changes that spreads across the cerebral cortex. Recently there has been a growing recognition that it may be an important pathophysiological event in a number of neurological disorders. In this paper, we describe a reaction-diffusion model of the extracellular potassium changes that are a central part of this process. Simulations with the model show that an appropriate stimulus evokes a moving wave of increased potassium with many similarities to that seen experimentally. The resultant model is a useful computational tool for future study of the effects of spreading depression on the cortex.

INTRODUCTION

Cortical spreading depression (CSD) is an expanding wave of temporarily suppressed electrical activity and biochemical disturbances that propagates across the cerebral cortex at a rate of about 2 – 5 mm/min (illustrated schematically in Fig. 1) [1, 3, 6, 10]. It can be initiated by topical application to the cortex of various chemicals (potassium, excitatory aminoacids, etc.), or mechanical/electrical stimuli. The exact physiological events involved in CSD are not completely understood, but the most generally accepted hypothesis is that the release of potassium ions (K^+), and possibly neurotransmitters such as glutamate, is the critical event. It is observed that as K^+ diffuses through the cortex, nearby regions first show a slow, small increase in extracellular K^+, followed by a dramatic rise once the K^+ level exceeds about 10 mM. The markedly elevated extracellular K^+ concentration depolarizes neurons and leads to suppression of their firing of action potentials.

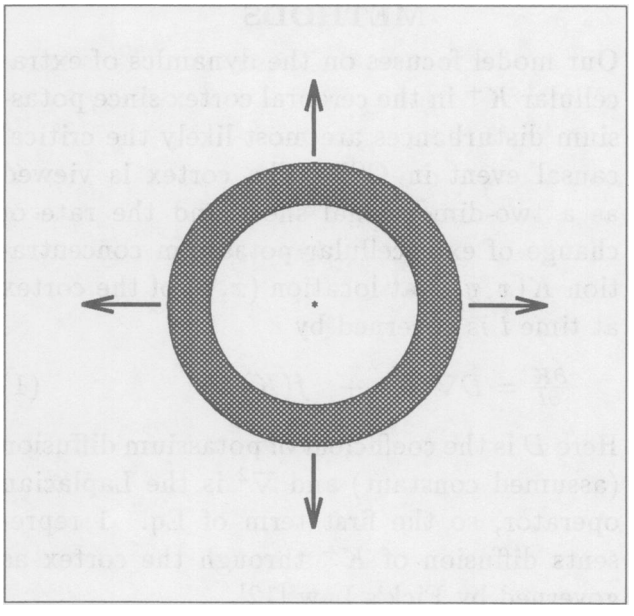

Figure 1: Annular wave of CSD (shaded) arising from a stimulus site (dot at center).

CSD has attracted attention recently due to suspicions that it may be an important pathophysiologic component of disorders such as migraine, cerebral ischemia and head trauma [5, 9, 16]. For example, it has been postulated that CSD may initiate migraine attacks and cause the associated aura [8]. In spite of this, there have been very few previous efforts to computationally or mathematically model CSD [1, 15, 17]. Because of the growing recognition of the clinical relevance of CSD, it is timely to develop a computational model that can be used to complement experimental work. Accordingly, we describe a model of the genesis and propagation of increased potassium during CSD and simulations that validate its behavior. The goal was to produce a model that was both robust to reasonable changes in parameters and computationally efficient when used with large, two-

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dimensional cortical regions. In the following, we first describe the mathematical model of CSD we have developed, and then present the results of numerical simulations with it. We conclude with a discussion contrasting our model with previous related work.

METHODS

Our model focuses on the dynamics of extracellular K^+ in the cerebral cortex since potassium disturbances are most likely the critical causal event in CSD. The cortex is viewed as a two-dimensional sheet and the rate of change of extracellular potassium concentration $K(x, y, t)$ at location (x, y) of the cortex at time t is governed by

$$\frac{\partial K}{\partial t} = D\nabla^2 K \quad + \quad f(K). \tag{1}$$

Here D is the coefficient of potassium diffusion (assumed constant) and ∇^2 is the Laplacian operator, so the first term of Eq. 1 represents diffusion of K^+ through the cortex as governed by Fick's Law [12].

The second term $f(K)$ in Eq. 1, which we take to be independent of cortical location and time, represents the local dynamics of extracellular potassium. These local dynamics must meet at least four requirements: homeostatic maintenance of resting extracellular potassium level $K_r > 0$ (approx. 3 mM in the cortex), a threshold $K_\theta > K_r$ beyond which elevated K triggers explosive subsequent growth in K, a ceiling $K_m > K_\theta$ above which K does not rise, and restoration to normal K levels that reflects post-wave intracellular resequestration of potassium. To capture these behaviors our model uses

$$f(K) = A(K - K_r)(K - K_\theta)(K - K_m)(K + 0.1) - rK \tag{2}$$

where $A < 0$ is a rate constant, and resequestration of potassium r is modeled as

$$\frac{\partial r}{\partial t} = B((K - K_r) - Cr) \tag{3}$$

where $0 < B << |A|$ and $C > 0$ are constants.

The quartic polynomial forming the first term in Eq. 2 satisfies the first three requirements outlined above. For example, if K is just above (below) K_r, then this polynomial is negative (positive), tending to return K to K_r (Eq. 1). The second term, $-rK$, provides for restoration of K to its resting value during the recovery phase. Eq. 3 represents the slow (B small) resequestration of potassium that rises in the face of increased K; as can be seen in Eq. 1 and 2, when r is elevated there is a tendency for K levels to fall. Our formal model expressed in Eqs. 1-3 is similar in form to, and in part inspired by, previous mathematical models of wave-like phenomena, such as calcium activation waves on the enclosing membranes of amphibian eggs [2, 7] and the FitzHugh-Nagumo model of action potentials in neurons [4, 11].

In the computer implementation of this model, both the spatial structure of the cerebral cortex and time are discretized. The cortex is represented as a two-dimensional array of elements, each of which represents a small volume of cortex (say 25 microns wide [13]). A hexagonal tessellation of the cortex is assumed, so each element has six immediately adjacent neighbor elements. Each cortical element i has its own extracellular potassium value K_i and resequestration value r_i governed by Eqs. 1-3. Initially, each element starts with $K_i = K_r$ and $r_i = 0$. This is a fixed point of the system (i.e., the model is initially in an equilibrium state) since with these values $\frac{\partial K_i}{\partial t} = 0$ and $\frac{\partial r_i}{\partial t} = 0$ for all elements i. The model's behavior is then studied numerically after perturbing it from this equilibrium state by simulating the external application of potassium to one or more elements j by raising the value K_j for those elements. In the simulation results described below, a time step of 0.25 is used, and a 100x100 element cortical region is modeled with opposite edges connected (forming a torus) to avoid edge effects. Parameter values used in the simulations reported here are D=0.75, A=-0.3, $K_r = 0.03$, $K_\theta = 0.2$, $K_m = 1.0$, B=0.0001,

and C=10.0. These parameter values, determined empirically, produce a good waveform and the K values obtained can be viewed as one-hundredth of actual extracellular K^+ concentration in mM units.

RESULTS

The key result of our simulations is that a localized area of elevated potassium evokes a traveling wave of markedly elevated potassium that slowly propagates in an expanding annular region. For example, clamping the K value of a hexagonal cluster of seven elements to $K = 1.0$ for 1000 ticks leads to a potassium wave as depicted schematically in Figure 1. These simulations verify that the formal model represented by Eqs. 1-3, when simulated in a discrete fashion, can generate potassium waves. Further, when such waves, traveling in opposite directions, collide with one another, they obliterate each other, just as occurs experimentally. A wave is followed by a refractory period. Wave speed approximated 0.2 elements per simulated time unit. If one takes simulated cortical elements to be 25 microns wide and calibrates simulated wave duration (Fig. 2, adjustable by varying B) with experimentally measured wave duration, the model's wave speed corresponds to roughly 5 mm/min, near the upper range of wave speeds observed experimentally.

Figure 2 illustrates the nature of the propagating potassium wave. The horizontal axis represents time, and the vertical axis represents the extracellular potassium concentration K (solid line) and recovery variable r (dashed line) of a single cortical element as the potassium wave reaches it. As potassium diffuses into the element, there is an initial slow rise in K, followed by a sudden dramatic rise, a gradually decreasing plateau, and a more rapid fall as the wave passes beyond the element. These features are similar to those seen experimentally.

To examine the stimulus required to evoke the potassium wave, we ran over 250 simulations varying the intensity, duration and size

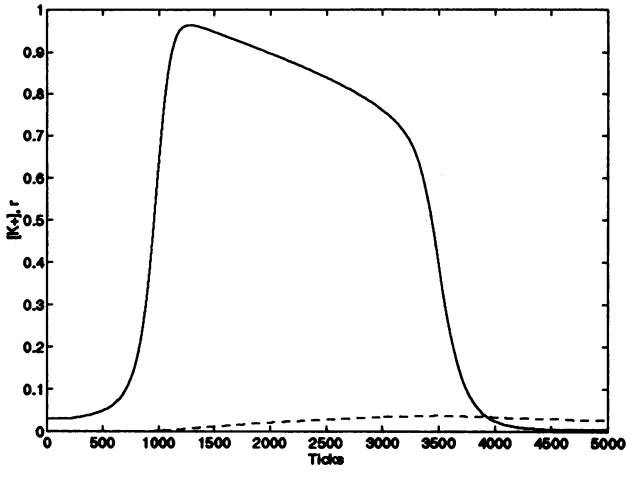

Figure 2: Extracellular potassium wave (solid line) and resequestration variable r (dashed line). Each "tick" is one iteration.

(1, 7, or 19 elements) of the hexagonal stimulus patch of elevated K. For all three stimulus sizes, a maximal stimulus ($K = K_m$) that persisted sufficiently long evoked a well-formed wave. For each patch size, however, there was a stimulus intensity $K < 1.0$ below which a maximal wave could not be evoked. As the patch size was increased, weaker and shorter duration stimuli were needed to elicit a maximal wave.

For example, to study the response to stimulus patches with seven elements, we varied the level of the clamped K from 0.0 to 1.0 and the duration of application of the stimulus from 100 to 5000 ticks (iterations). We ran approximately 100 simulations sampling points throughout the stimulus parameter space to get a general picture of the model's behavior, and then focused additional simulations on the interesting regions. In all of these simulations, one of two events occurred: either a strong sustained wave like that shown in Fig. 2 was evoked, with $K > 0.9$, or no wave resulted, and the potassium remained below 0.15 except in the immediate neighborhood of the stimulus. No intermediate strength waves were observed. The boundary between the two behaviors was quite sharp (line in Figure 3). All points on or above the line in Fig.

3 resulted in a wave like that shown in Fig. 2; all points below the line produced no wave. For this patch size, no wave resulted for stimuli with $K < 0.69$, even when held for 5000 timesteps. For $K \geq 0.69$, waves formed whenever the stimulus was clamped for a sufficient length of time. The one element and nineteen element patch size simulations produced similar results, with the one element patch requiring stronger and longer stimuli to evoke a wave, and the nineteen element patch producing a wave with weaker and shorter stimuli. Increases in the intensity or duration of the stimulus above the minimum threshold resulted in the wave being evoked sooner, but did not change the overall shape of the wave.

We also examined the total potassium added to the system and its relationship to the threshold for evoking a wave. The total potassium added was determined by subtracting, at each timestep, the K value that each stimulus element would have at the next time instant (from Eqs. 1 - 3) from the clamped K value, and summing this calculation for the duration of the stimulus. It was found that the lower the level of clamped K, the more total potassium had to be added to the system to evoke a wave.

DISCUSSION

The growing interest in the clinical relevance of CSD has motivated us to develop a computational model of CSD so that its properties and effects can be studied theoretically. In this paper we have examined an important, presumably causative component of CSD, the spreading wave of dramatically increased extracellular potassium concentration. We showed that it can be simulated by a two-dimensional, reaction-diffusion system. As described above, numerical simulations based on the model confirm that it produces a propagating disturbance having several features similar to those seen experimentally.

Our model can be contrasted with three previous efforts to model various aspects of

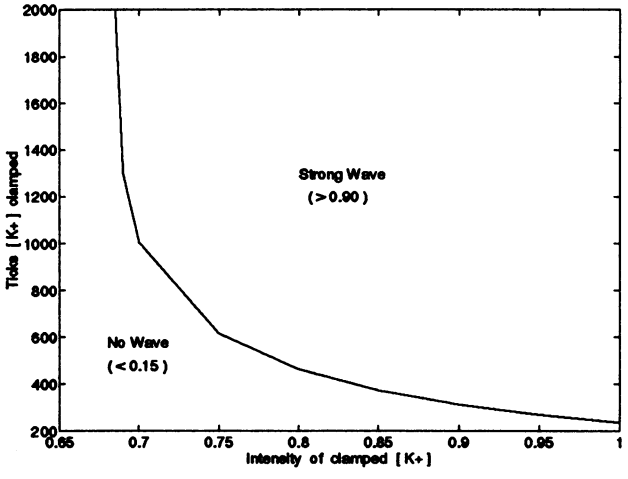

Figure 3: Threshold for evoking potassium wave in terms of intensity and duration of stimulus for a seven element hexagonal stimulus patch. Only stimuli on or above the line evoke a wave like that in Figure 2.

CSD. One previous cellular automata model represented the cortex as a two-dimensional spatial array of elements as we have done, but each element could be in only one of three discrete states (quiescent, depressed, or refractory) [15]. Elements changed state according to transition rules that did not explicitly represent physiological causative factors such as extracellular K^+ concentration. Our model differs in using a continuous-valued K^+ level at each element whose value is governed by two differential equations (Eqs. 1, 3).

Two other previous models of CSD used continuous representations of element states and reaction-diffusion equations as we have, but both considered only one-dimensional spatial distributions and used different local dynamics for extracellular K^+ (i.e., different formulas for $f(K)$). The earliest of these two models, attributed to A. L. Hodgkin, represented a wave of rising extracellular K^+ concentration but no restoration phase, and was apparently never simulated numerically [1]. The other one-dimensional model represented not only multiple intracellular and extracellular ionic changes, but also release of neurotransmitters and membrane potential [17].

This latter detailed model is more physiologically complete than the model we have developed, but produces a temporal waveform that is qualitatively less similar to experimental data than ours (Figure 2). Its complexity and computational expense would make it difficult to use in large, two-dimensional cortical simulations.

The model we have described in this paper will be used in future studies to learn more about CSD and its effects on cortical physiology. It will be extended to capture other presumably secondary biochemical changes of CSD, and will be combined with a computational model of cortical neural activity [13]. We intend to apply the validated model to study computationally various hypotheses about the role of CSD in neurological disorders such as stroke and migraine. Thus, from the perspective of modeling in general, our results support recent suggestions that computational models have an underutilized role to play in studying neurological disorders [14].

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